Toxicokinetics of BDE 47 in Rodents

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Introduction

2,2',4,4'-tetrabromodiphenyl ether (BDE 47) is a specific polybrominated diphenyl ether (PBDE) in a class of brominated flame retardants (BFRs) commonly used in a wide variety of highly flammable consumer goods. Concern for the effects of PBDEs has increased significantly in recent years as their presence has been detected in environmental samples and in human tissues at steadily increasing concentrations. Despite its small contribution to PBDE global production and usage, BDE 47 is the major congener found in environmental samples and human tissue. Limited toxicology studies suggest that BDE 47 is a developmental neurotoxicant and an endocrine disrupter (Eriksson et al. 2001, Hallgren et al. 2001).

The widespread production and use of BDE 47, strong evidence of increasing contamination of the environment, wildlife, and people, and limited knowledge of potential toxicological effects heightens the importance of establishing a basic foundation of information on this chemical. Several data gaps exist and must be investigated in order to evaluate the human health risk of BDE 47. *In an effort to fill in some of these data gaps, we will research and determine the descriptive kinetic parameters, including absorption, distribution, metabolism, and excretion (ADME) of BDE 47 in rodents. We hypothesize that BDE 47 is a persistent, bioaccumulative, and toxic chemical that has toxicokinetic properties similar to other polyhalogenated aromatic hydrocarbons. We further believe that the primary means of toxicity to humans is through upregulation of UGT and subsequent decreases in thyroid hormones during critical developmental periods; and will therefore investigate both the potential for UGT upregulation in human hepatocytes as well as the pathway involved in its induction by BDE 47.*

Specific Aims and Methods

•**Aim1: To characterize basic kinetic parameters in rodents.** We will determine the basic descriptive kinetic parameters of an acute dose of BDE 47 in rodents. Four phases, dose/response, route of exposure, time course, and biliary elimination will provide data for us to establish an understanding of the ADME.

•**Aim 2: To compare UGT induction potential between species.** Primary human and rodent hepatocytes, along with *in vivo* tissues from Aim 1, will be used to compare the effects of BDE 47 exposure on the induction UGTs. We will expose hepatocytes to BDE 47 and assay for changes in the conjugation of T4 by UGT (UGT/T4 activity) and use RT-PCR to identify specific mRNA involved in an upregulation pathways, such as nuclear receptors AhR, PXR, and CAR, as well as specific UGT isozymes involved in upregulation.

Aim 3: To investigate the toxicokinetics of BDE 47 in a developmental model. In an effort to link known neurotoxic effects in developing pups to maternal and neonatal exposure, we will examine the toxicokinetics of BDE 47 during critical time periods in development.

Aim 4: To apply a physiologically based pharmacokinetic (PBPK) model to BDE 47.
We will use a PBPK model to explore and predict the behavior of this BFR both independently and in a mixture, and extrapolate this model to humans for use in assessing risk associated with BDE 47.

Results

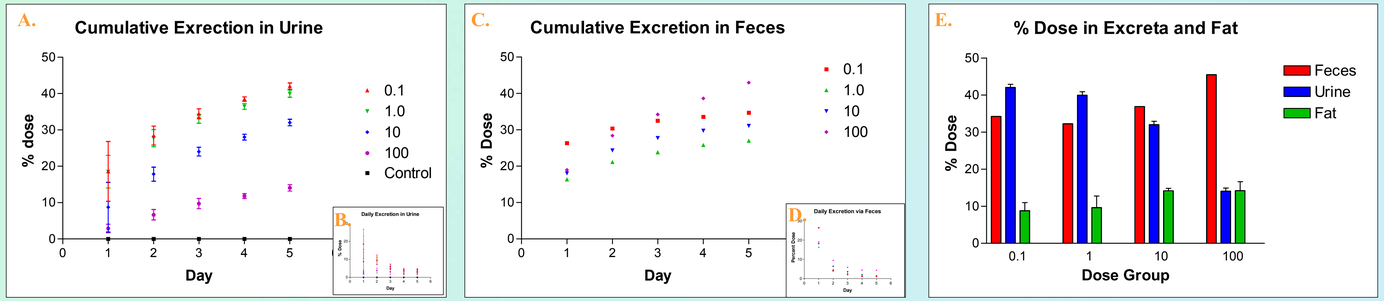
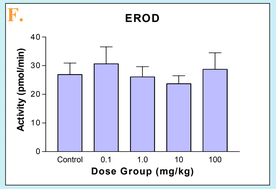


Figure 1. A) Cumulative urinary excretion of BDE 47 in female, C57BL6 mice based on residual radioactivity five days following a single, oral exposure. Values presented as percent of dose administered. B) Daily urinary excretion. C) Cumulative fecal excretion. D) Daily fecal excretion. E) Preliminary mass balance analysis, based on % of dose, in excreta and adipose tissue. F)EROD, a specific CYP1A substrate, activity.



Conclusions and Impact

•The disposition of BDE 47 in mice is dependent on dose, and absorption and metabolism may be key factors in determining body burden *in vivo.*
•Data from this study will allow us to design studies that will determine the required dose needed for maternal body burden to doses used in developmental neurotoxicity studies.

Future Direction

The results of this pilot study have generated a multitude of directions that need to be explored concerning the toxicokinetics of BDE 47 in rodents. One of the first will include analysis of the excreta to screen for potential metabolites of BDE 47, which would indicate the ability for mice to metabolize this chemical. The next dosing phase will compare routes of exposure (oral, dermal, i.v., and i.t), which will determine the percent of absorption in vivo. This will be followed by a time course study that will provide information on the half life of BDE 47 in mice. After determining the basic toxicokinetic parameters in an adult model, absorption, distribution, metabolism, and elimination, we will explore the same parameters in a developmental model. Limited toxicology studies suggest that BDE 47 is a developmental neurotoxicant and an endocrine disruptor, which underlies the need to understand the kinetics of this flame retardant in developing offspring. All data will then be incorporated into a physiologically based pharmacokinetic model which will allow for prediction and extrapolation of BDE 47 kinetics in humans.